Incidence of Tetanus and Diphtheria in Relation to Adult Vaccination Schedules

SUPPLEMENTARY DATA

Table of Contents

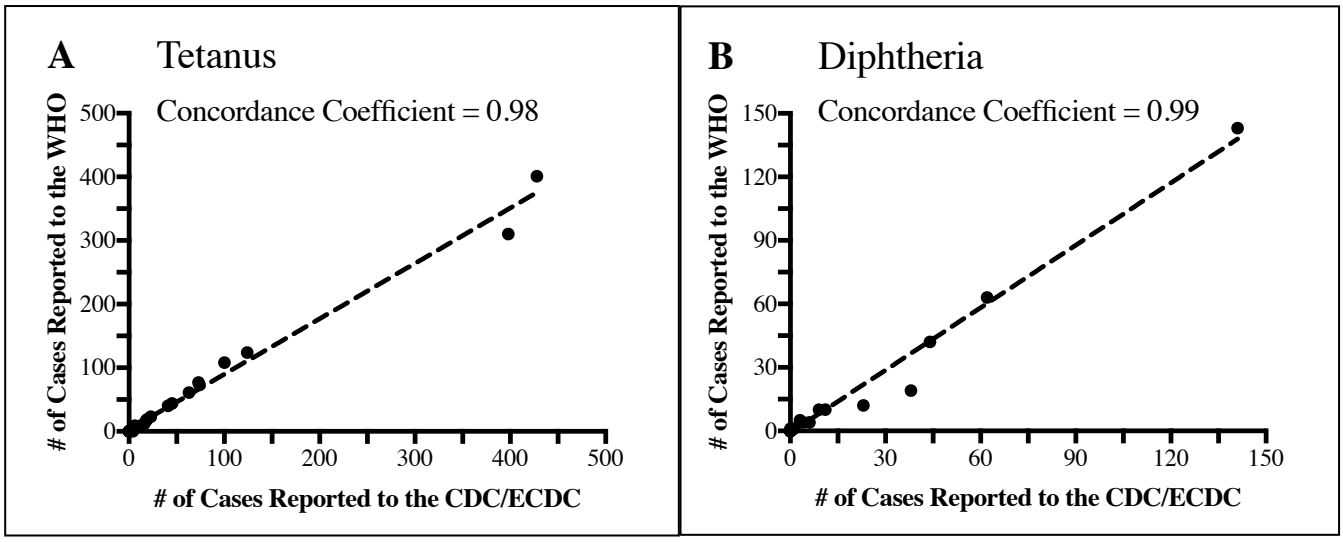
Supplementary Methods

Data sources and statistical analysis

An observational cohort study was conducted using secondary sources from the World Health Organization Vaccine-Preventable Diseases Monitoring System [1] and population data calculated by World Bank [2]. The total number of cases reported to WHO from each country were compared with available reports obtained from the CDC/ECDC and were found to have 98% and 99% concordance for tetanus and diphtheria reporting, respectively (Supplemental Figure 1). To statistically compare disease incidence rates between countries that vaccinate adults and those that do not routinely vaccinate adults, each country was considered as an observational unit. For each observational unit, the number of incidence cases represent the total number of cases from 2001-2016, and the total number of person-years from 2001-2016 was used as the Poisson offset. Similar analyses were also performed for 1-year interval data in 2015 and 2016 to compare the most recent yearly incidence rates. Specific years in which the WHO did not receive reports from a particular country were excluded from the calculated incidence rates. Overall, WHO data was available for 82% and 93% of the years in question for tetanus and diphtheria, respectively, and together this provided a total of 11.6 billion person-years of tetanus incidence data and 13.4 billion person-years of diphtheria incidence data. The annual number of reported tetanus and diphtheria cases were transferred from the WHO database to Excel files using double-data entry. To determine the incidence rates of disease, the all-age population of a country as a mid-year estimate by the World Bank was used as the denominator. The World Bank database includes the total population of each country from 1960 to 2016 and used the de facto definition of population, which includes all people in the country at the reference time-point regardless of their legal status or citizenship. The WHO database provided the number of reported cases for a variety of vaccine-preventable diseases including tetanus (total and neonatal) and diphtheria from 1980-2016. For visualizing longitudinal trends in the incidence of each disease from 2001 to 2016, the total number of cases for each available year in 31 North American and European countries were divided by the total population of the country/countries within each group to calculate the incidence per million person-years. Countries were chosen originally from publications by Weinberger [3] and Lee & Choi [4]. Although the number of tetanus or diphtheria cases reported to the WHO may be subject to some degree of inaccuracy or under-reporting in countries that do not have established disease surveillance systems [5], countries in North America and Europe have well-functioning immunization and surveillance programs in place [5, 6] and were chosen in order to provide a representative assessment of tetanus and diphtheria disease incidence rates among countries that do or do not implement routine adult booster vaccination policies. Upon further review of historical country-specific adult vaccination schedules, Spain was excluded from analysis due to removing their decennial adult booster recommendation during the 2001-2016 period of observation (i.e., 2009 [7]) and Norway was excluded due to unclear recommendations during 2001-2016. Overall, robust incidence rate estimates for each group were obtained by dividing the total number of cases from 2001-2016 in all countries by the total number of person-years from each of the countries within each group from 2001-2016 along with determining 95% exact Poisson confidence intervals. A univariate Negative Binomial Regression (NBR) model was used to compare incidence rates between the two groups. In diphtheria analysis, Latvia was suspected to be a potential influential observation by Cooks distance and sensitivity analysis was performed both including and excluding Latvia in the univariate NBR. Data analysis was performed using R version 3.4.2. The P-value <0.05 was considered statistically significant.

In this study, the data pertaining to 2,819 cases of tetanus and 572 cases of diphtheria was collected through the WHO/UNICEF Joint Reporting Form, which is sent to all WHO Member States and then reviewed for completeness and consistency. The WHO defines a case of adult tetanus as painful muscular contractions,

including contractions in the face such as trismus (lockjaw) or *risus sardonicus* (spasm of facial muscles that resembles a forced grin). A history of injury is also required although tetanus may occur in patients who do not remember a specific incident [5]. The WHO characterizes diphtheria as "an illness by laryngitis or pharyngitis or tonsillitis, and an adherent membrane of the tonsils, pharynx and/or nose" [8].



Supplemental Figure 1: Concordance of Cases Reported to the WHO and CDC/ECDC
The total number of tetanus (A) and diphtheria (B) cases reported to the World Health Organization (WHO) from 2001-2016 were compared to publicly available data from the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC). The CDC had data available from 2001-2016 for tetanus and from 2001-2015 for diphtheria. ECDC data was available from 2005-2016 for tetanus and 2006-2016 for diphtheria. Each plotted data point represents an individual country in which the total cases of tetanus or diphtheria were reported to the WHO and CDC/ECDC from 2001-2016. Only years in which a country reported to both the WHO and the CDC/ECDC were included in the data used for concordance analysis. Concordance between the total number of cases reported to the WHO and the CDC/ECDC was determined using Lin's concordance correlation coefficient.

WHO: https://apps.who.int/immunization_monitoring/globalsummary
CDC: https://www.cdc.gov/mmwr/mmwr_nd/index.html
ECDC: https://ecdc.europa.eu/en/tetanus/surveillance-and-disease-data/annual-epidemiological-report

Supplementary Discussion

Glycoconjugate vaccines formulated with tetanus or diphtheria toxoid

In addition to standard tetanus- and diphtheria-containing vaccines, there are a number of conjugate vaccines that utilize tetanus toxoid, diphtheria toxoid, or Cross Reacting Material 197 (CRM197, a non-toxic diphtheria toxin mutant protein) as carrier proteins to improve the immunogenicity of polysaccharide vaccines. In most cases, these vaccines have not been formally tested for their ability to induce protective immune responses to these carrier proteins [9]. One study tested 5 different commercially available glycoconjugates for protective immunity against tetanus and diphtheria according to the European Pharmacopoeia [9]. The tetanus toxoid carrier protein-based meningococcal vaccine, Menitorix, protected guinea pigs from lethal challenge with tetanus toxin whereas the diphtheria toxoid carrier protein-based meningococcal vaccine, Menactra, and the diphtheria toxoid carrier protein-based pneumococcal vaccine, Synflorix both protected guinea pigs from lethal diphtheria challenge. In contrast, meningoccal vaccines based on CRM197 carrier protein such as Menveo and Mejugate failed to protect animals from lethal diphtheria challenge. This indicates that some, but not all glycoconjugate vaccines have the potential to induce protective antitoxin immunity and this underscores the point that different carrier proteins prepared with different conjugation technologies will need to be tested on a case-by-case basis to determine their ability to induce protective immune responses *in vivo*. With the exception of the childhood vaccine against *Haemophilus influenzae* type b (Hib), most glycoconjugate vaccines were still in clinical trials in the early to mid 2000's [10] before obtaining regulatory approval for commercial use. Based on the early trends in 2001, 2002, 2003, etc. describing the incidence of tetanus (Main text, Figure 1A) and diphtheria (Main text, Figure 2A), there were no major differences in the incidence of these two diseases between countries that did or did not recommend routine adult booster immunization with standard tetanus- and diphtheria-containing vaccines. This suggests that although glycoconjugate vaccines utilizing tetanus- and diphtheria toxoid-based carrier proteins have the potential to further boost antitoxin immunity, they are unlikely to be required since disease incidence was already similar between Group 1 and Group 2 countries prior to the approval and widespread use of these vaccines among the 31 countries described in this current study.

Risk:Benefit ratio of adult booster vaccination programs

In addition to determining the impact of adult vaccination on the incidence of vaccine-preventable disease, it is important to compare the overall cost associated with modifying the vaccination schedule and the number of vaccine-associated adverse events that may be reduced or eliminated if the WHO vaccination guidelines were adopted. Td (tetanus, diphtheria) vaccination is safe and serious adverse events (SAEs) are rare. However, the relative risk:benefit ratio is an important aspect to consider when revising any vaccination schedule since a reduction in the number of administered vaccine doses will result in a parallel reduction in vaccine-associated AEs and SAEs. For example, a Vaccine Safety Datalink (VSD) cohort study estimated that the risk of a medically attended local reaction among adults occurs at a rate of 87 per 100,000 Td vaccinations [11]. When multiplied by approximately 15.2 million adult vaccinations administered annually in the U.S. [12], this suggests that approximately 13,200 patients may be seen by a healthcare professional each year due to local Td vaccine-associated AEs. After assessment of 436,828 Td vaccinations, validated review of 713 individual medical charts from adolescents and young adults identified at least 23 patients who were diagnosed with cellulitis (5.27 per 100,000 vaccinations) and 2 patients diagnosed with ulcerated lesions (0.478 per 100,000 doses) [11]. When multiplied by 15.2 million vaccinations, this indicates that up to 800 cases of cellulitis and 73 cases of ulcerated lesions may be associated with Td vaccinations in the U.S. each year. Although passive surveillance through VAERS (Vaccine Adverse Event Reporting System) indicates a lower rate of cellulitis following TDaP vaccination

(~33 cases/15.2 million vaccinations) [13], this form of AE monitoring may be limited by under-reporting [14]. On the other hand, the results of the VSD cohort study are considerably lower than an active surveillance study of adult Td vaccinations which found a number of serious adverse events including swelling of the arm below the elbow (1.1%) and abscess or infection (0.7%) among recipients of needle-injection or jet injector vaccinations [15]. A study involving TDaP booster vaccination of healthcare personnel found that 4.2% of 805 subjects who completed a daily survey reported severe swelling (≥48.52 mm) at the injection site and 1.3% of 880 respondents reported seeing a healthcare provider because of symptoms experienced after vaccination [16]. Vaccine-associated severe allergic events are estimated to occur at a rate of 0.16/100,000 vaccinations (24 cases/15.2 million vaccinations) [17] and vaccine-associated brachial plexus neuritis is estimated at 0.5-1 case/100,000 vaccinations (7.6-15.2 cases/15.2 million vaccinations) [17]. Although there have been some reports of tetanus vaccine-associated Guillain-Barré syndrome (GBS), population level studies have not supported this association [18]. Bearing in mind that attribution of rare systemic adverse events directly to Td vaccination is more difficult to interpret than analysis of local vaccination site reactions, these nevertheless represent potential AEs that can be avoided if the total number of Td vaccinations were reduced by modifying the adult vaccination schedule.

Vaccine-associated healthcare costs

In addition to an improved risk:benefit ratio, vaccine-associated healthcare costs could be sharply reduced if the WHO vaccination guidelines were implemented (Supplemental Table 1). Although only 63-64% of adults in the U.S. report complying with their recommended decennial booster vaccinations [19, 20], there are still approximately 15.2 million Td vaccinations performed each year [12]. Based on these numbers and the cost of both the vaccine and vaccine administration, a total of $1.03B (range, $0.68B to $1.39B) could be saved each year in the United States alone if the WHO guidelines were followed. These savings could then be used to focus financial resources on unvaccinated, under-vaccinated and vulnerable at-risk populations as well as other health care priorities.

Supplemental Table 1: Estimated Annual Cost of Adult Tetanus and Diphtheria Immunizations in the U.S.

Price per Dose[a] ($)	Price to Administer Vaccine[b] ($)	Total Cost ($)	# of Adult Vaccinations per Year[c]	Total Cost per Year ($)[d]
25.12	22.31 (low)	47.43	15,200,000	683,000,000
25.12	74.42 (high)	99.54	15,200,000	1,390,000,000
			Avg Total Cost	**1,030,000,000**

[a]Private sector cost per dose as reported in 2019 by the CDC [21].

[b]Estimated cost associated with administering a vaccine in different sized medical practices in 2001 [22]. Prices were adjusted at a 2% inflation rate each year to estimate 2019 prices.

[c]Estimated number of adult vaccinations per year in the United States [12].

[d]The total cost of Td vaccination per year was determined by multiplying the sum of the cost of the vaccine itself plus the cost of administering the vaccine, by 15.2 million vaccinations per year. Calculations may differ due to rounding error.

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